CLAIMS

1. A method of treating a patient suffering from poisoning or at risk of poisoning by a clostridial toxin wherein a SNARE (soluble (*N*-ethylmaleimide-sensitive fusion protein)-attachment protein receptor) is supplied to a cell of the patient, wherein the SNARE is resistant to proteolysis by the said clostridial toxin (toxin-resistant SNARE) and/or is capable of inhibiting the clostridial toxin (toxin-inhibitory SNARE).

2. The use of a SNARE (soluble (*N*-ethylmaleimide-sensitive fusion protein)-attachment protein receptor), or of a recombinant polynucleotide capable of expressing the said SNARE in the manufacture of a medicament for the treatment of a patient suffering from poisoning or at risk of poisoning by the said clostridial toxin, wherein the SNARE is resistant to proteolysis by the said clostridial toxin (toxin-resistant SNARE) and/or is capable of inhibiting the clostridial toxin (toxin-inhibitory SNARE).

3. A method of reversing the inhibition of exocytosis in a cell caused by contact of a clostridial toxin with the said cell, wherein a SNARE is supplied to the said cell not before contact of the said clostridial toxin with the said cell, wherein the SNARE is resistant to proteolysis by the said clostridial toxin (toxin-resistant SNARE) and/or is capable of inhibiting the clostridial toxin (toxin-inhibitory SNARE).

4. The method or use of any one of claims 1 to 3 wherein the said SNARE that is resistant to proteolysis by the said clostridial toxin is synaptosomal-associated polypeptide of 25 kDA (SNAP-25) that is resistant to proteolysis by the said clostridial toxin.

5. The method or use of any one of claims 1 to 3 wherein the said SNARE that is resistant to proteolysis by the said clostridial toxin is syntaxin 1 or synaptobrevin that is resistant to proteolysis by the said clostridial toxin.

6. The method of any of the preceding claims wherein the SNARE that is capable of inhibiting the clostridial toxin (toxin-inhibitory SNARE) is synaptosomal-associated polypeptide of 25 kDA (SNAP-25) that is capable of inhibiting the clostridial toxin.

7. The method of any of the preceding claims wherein the SNARE that is capable of inhibiting the clostridial toxin (toxin-inhibitory SNARE) is a SNARE in which the residue immediately N-terminal to the clostridial toxin cleavage site is replaced by a cysteine residue.

8. The method or use of any of claims 1 to 4, 6 to 7 wherein the said clostridial toxin is botulinum toxin A (BoNT/A).

9. The method or use of claim 4 wherein the said SNARE is resistant to proteolysis by botulinum toxins A, B and C1 (BoNT/A, BoNT/B and BoNT/C1).

10. The method or use of claim 8 or 9 when dependent on claim 4 wherein the said SNARE is a variant of SNAP-25 in which the residue equivalent to residue 197 and/or the residue equivalent to residue 198 of full length SNAP-25 are replaced by a residue other than Gln or a residue other than Arg, respectively.

11. The method or use of claim 10 wherein the residue equivalent to R198 of full length human SNAP-25 is replaced by a residue other than R, for example A, T, K, H or W and the residue equivalent to residue Q197 of full length SNAP-25 is Q or is replaced, for example by A, K or W.

12. The method or use of any of the preceding claims wherein the said SNARE that is resistant to proteolysis by the said clostridial toxin is capable of performing substantially the equivalent function to a SNARE present in the cell that is capable of being cleaved in the said cell by the said clostridial toxin.

13. The method or use of any of claims 1, 2, 4 to 12 wherein the patient has or is at risk of botulism.

14. The method or use of any of claims 1, 2, 5, 7 or 12 wherein the patient has or is at risk of tetanus.

15. The method or use of any of claims 1, 2, 4 to 14 wherein the patient is an infant.

16. The method of any of claims 1, 2, 4 to 15 further comprising the steps of determining the type of the said clostridial toxin from which the patient is suffering and of selecting an appropriate SNARE that is resistant to proteolysis by the determined clostridial toxin and/or is capable of inhibiting the determined clostridial toxin for use in the treatment.

17. The method of any of claims 1, 2, 4 to 16 further comprising the steps of treating the patient with an inhibitor of the said clostridial toxin.

18. The method of claim 17 wherein the inhibitor of the said clostridial toxin is a SNARE that is capable of inhibiting the said clostridial toxin (toxin-inhibitory SNARE) or a recombinant polynucleotide capable of expressing the said toxin-inhibitory SNARE, for example as defined in any one of claims 6 to 8.

19. A method of treating a patient in need of inhibition of SNARE-dependent exocytosis from a cell capable of performing SNARE-dependent exocytosis wherein a

fragment, variant, fusion or derivative of a SNARE or a fusion of a said fragment, variant or derivative (inhibitory SNARE) that is capable of inhibiting SNARE-dependent exocytosis is supplied to the said cell of the patient.

20. The use of (1) a fragment, variant, fusion or derivative of a SNARE or a fusion of a said fragment, variant or derivative (inhibitory SNARE) that is capable of inhibiting NARE-dependent exocytosis or (2) a recombinant polynucleotide capable of xpressing a fragment, variant, fusion or derivative of a SNARE or a fusion of a said fragment, variant or derivative (inhibitory SNARE) that is capable of inhibiting SNARE-dependent exocytosis in the manufacture of a medicament for the treatment of patient in need of inhibition of SNARE-dependent exocytosis from a cell capable of performing SNARE-dependent exocytosis.

21. The method of claim 19 or use of claim 20 wherein the said inhibitory SNARE is a fragment derivable by cleavage of a SNARE by a clostridial toxin, for example BoNT/A.

22. The method or use of claim 21 wherein the said inhibitory SNARE is a fragment derivable by cleavage of SNAP-25 or a variant thereof by BoNT/A.

23. The method or use of claim 22 wherein the said inhibitory SNARE consists of residues identical to residues 1 to 197 of full length SNAP-25 or a variant thereof.

24. The method or use of any one of claims 19 to 23 wherein the cell is a nerve cell, adreno-chromaffin cell or insulin-secreting cell.

25. A SNARE polypeptide for use in medicine.

26. A molecule which comprises a SNARE polypeptide or toxin-resistant or toxin-inhibitory SNARE polypeptide or inhibitory SNARE polypeptide as defined in any of the preceding claims and a further portion.

27. The molecule of claim 26 wherein the said further portion is capable of promoting cellular uptake of the molecule or the said SNARE polypeptide or toxin-resistant or toxin-inhibitory SNARE polypeptide or inhibitory SNARE polypeptide.

28. The molecule of claim 26 or 27 wherein the said further portion is an inactive clostridial neurotoxin having specificity for a target nerve cell.

29. A polypeptide that is a variant, fragment, derivative or fusion of SNAP-25 that is resistant to cleavage by BoNT/A or is capable of inhibiting BoNT/A wherein (1) the residue equivalent to residue Q197 of full length SNAP-25 is replaced by A or W and the said fragment is at least 18 amino acids in length or (2) the residue equivalent to residue R198 of full length SNAP-25 is replaced by H or W, and the said fragment is at least 18 amino acids in length or (3) the residue equivalent to residue Q197 of full length SNAP-25 is replaced by A, K or W and the residue equivalent to R198 of full length SNAP-25 is replaced by a residue other than R, for example A, T, K, H or W or (4) the residue equivalent to residue R198 of full length SNAP-25 is replaced by a residue other than R, for example A, T, K, H or W wherein residues equivalent to one or more of amino acids 203 to 206 are not present or (5) the polypeptide is also resistant to cleavage by BoNT/E and BoNT/C or (6) the residue equivalent to residue Q197 of full length SNAP-25 is replaced by C.

30. A polypeptide consisting of residues identical to residues 1 to 198, 199, 200 or 201 of full length SNAP-25 or a variant thereof, or a fusion either thereof.

31. A SNARE in which the residue immediately N-terminal to a clostridial toxin cleavage site (for example BoNT/A cleavage site) is replaced by a cysteine residue.

32. A toxin-resistant or toxin-inhibitory SNARE or inhibitory SNARE as defined in any of the preceding claims or a molecule or polypeptide according to any one of claims 26 to 31 for use in medicine.

33. A nucleic acid encoding a polypeptide according to claim 29 or 31 or molecule according to claim 26, 27 or 28 or toxin-inhibitory SNARE as defined in any of the preceding claims.

34. A nucleic acid suitable for expressing a polypeptide according to claim 29 or 30 or 31 or molecule according to claim 26, 27 or 28 or toxin-inhibitory SNARE as defined in any of the preceding claims.

35. A method of making a polypeptide according to claim 29 or 30 or 31 or molecule according to claim 26, 27 or 28 or toxin-inhibitory SNARE as defined in any of the preceding claims, the method comprising culturing a host cell comprising a nucleic acid according to claim 34, and isolating said polypeptide or molecule from said host cell.

36. The method or use of any one of claims 1 to 24 wherein the said toxin-resistant or toxin-inhibitory SNARE or inhibitory SNARE is supplied to the said cell by means of expression of the said toxin-resistant or toxin-inhibitory SNARE or inhibitory SNARE in the cell.

37. A recombinant polynucleotide encoding a SNARE or a variant, fragment, derivative or fusion thereof for use in medicine.

38. A recombinant polynucleotide encoding a toxin-resistant or toxin-inhibitory SNARE or inhibitory SNARE as defined in any of the preceding claims or a nucleic acid according to claim 33 or 34 for use in medicine.

39. A gene therapy construct comprising a recombinant polynucleotide or nucleic acid as defined in claim 37 or 38.

40. A gene therapy delivery system comprising an inactive clostridial neurotoxin having specificity for a target nerve cell and a polynucleotide comprising a target nerve cell-specific promoter.

41. The gene therapy delivery system of claim 40 wherein the inactive clostridial neurotoxin has specificity for a cholinergic neuron and the target nerve cell-specific promoter is specific for a cholinergic neuron.

42. A gene therapy construct according to claim 39, further comprising an inactive clostridial neurotoxin having specificity for a target nerve cell.

43. A gene therapy construct according to claim 42 further comprising a target nerve cell-specific promoter.

44. A pharmaceutical formulation comprising a polypeptide as defined in claim 25, toxin-resistant SNARE or inhibitory SNARE, molecule or polypeptide as defined in claim 32 or polynucleotide as defined in claim 37 or 38 together with one or more acceptable carriers.

45. A kit of parts comprising (1) means for determining the type of clostridial, for example botulinum, toxin from which a patient is suffering or means for determining

that a patient is suffering from a particular type of clostridal, for example botulinum, toxin and (2) a toxin-resistant and/or toxin-inhibitory SNARE as defined in claim 1 or recombinant polynucleotide capable of expressing said toxin-resistant or toxin-inhibitory SNARE.

46. A kit of parts comprising (1) a toxin-resistant and/or toxin-inhibitory SNARE or recombinant polynucleotide capable of expressing said toxin-resistant SNARE as defined in claim 1 and (2) an inhibitor of the clostridial toxin to which the said toxin-resistant SNARE is resistant.

47. Any novel method of treatment, use, polypeptide, molecule or nucleic acid as herein disclosed.